A New and Convenient Method for the Synthesis of 1,3-Disubstituted 4,6,6-Trimethyl-1,6-dihydropyrano[2,3-*c*]pyrazoles

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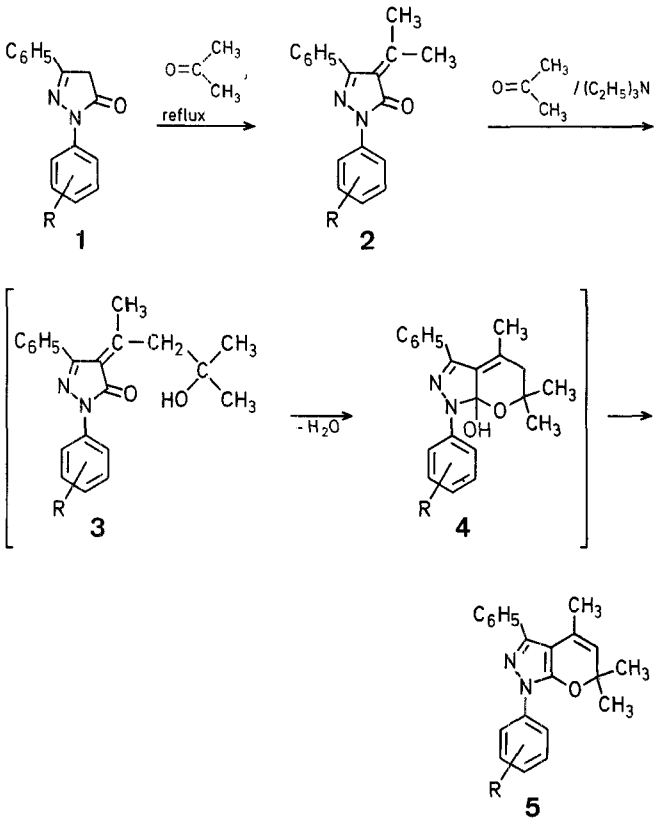
There are several examples methods for the preparation of 1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazoles[1-5], 1,4-dihydropyrano[2,3-*c*]pyrazoles[6,7,8], and 6-oxo-1,6-dihydropyrano[2,3-*c*]pyrazoles[9,10]. However to our knowledge, an efficient synthesis of 1,6-dihydropyrano[2,3-*c*]pyrazoles has not been reported so far. In the course of our investigations on anti-inflammatory compounds containing pyrazole rings, we found a novel and convenient preparation of the 1,6-dihydropyrano[2,3-*c*]pyrazole skeleton.



Reaction of 2-aryl-5-phenyl-3-oxo-3,4-dihydro-2*H*-pyrazoles **1a–f** with acetone at reflux gives the corresponding 2-aryl-4-(1-methylethylidene)-3-oxo-5-phenyl-3,4-dihydro-2*H*-pyrazoles **(2a–f)** in nearly quantitative yield (Table 1). Treatment of compounds **2a–f** with triethylamine in acetone at reflux results in cyclocondensation which probably proceeds via the not isolated 1-aryl-1a-hydroxy-4,6,6-trimethyl-3-phenyl-1,1a,5,6-tetrahydropyrano[2,3-*c*]pyrazole intermediates **4a–f** to give the 1-aryl-4,6,6-trimethyl-3-phenyl-1,6-dihydropyrano[2,3-*c*]pyrazoles **5a–f** as the final products. The structure of products **5a–f** is supported by the I.R.- and ^{1}H-N.M.R. spectra (Table 2).

4-(1-Methylethylidene)-2,5-diphenyl-3-oxo-3,4-dihydro-2*H*-pyrazole (2a); Typical Procedure:

A solution of 2,5-diphenyl-3-oxo-3,4-dihydro-2*H*-pyrazole (**1a**; 2.36 g, 10 mmol) in dry acetone (150 ml) is refluxed for 12 h. The mixture is then evaporated in vacuo at room temperature to give a dark brown solid, which is recrystallized from ethanol to give **2a**; yield: 2.50 g (90%); m.p. 116–117 °C.

$C_{18}H_{16}N_2O$	calc.	C 78.23	H 5.84	N 10.14
(276.3)	found	78.48	5.70	10.30

M.S.: *m/e* = 276 (M^+, 100%); 261 (95).

U.V. (C_2H_5OH): λ (logε) = 259 (4.20); 385 nm (2.91).

1,3-Diphenyl-4,6,6-trimethyl-1,6-dihydropyrano[2,3-*c*]pyrazole (5a); Typical Procedure:

A solution of **2a** (2.76 g, 10 mmol) and dry triethylamine (10.10 g, 100 mmol) in acetone (150 ml) is refluxed for 24 h. The solvent is then removed in vacuo at room temperature to give a dark brown oily resi-

Table 1. 2-Aryl-4-(1-methylethylidene)-3-oxo-5-phenyl-3,4-dihydro-2*H*-pyrazoles **(2a-f)**

2	R	Yield[a] [%]	m.p. [°C]	Molecular Formula[b]	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	H	90	116–117°	$C_{18}H_{16}N_2O$ (276.3)	1690, 1600	1.93 (s, 3H); 2.62 (s, 3H); 7.6–8.1 (m, 10H)
b	2-CH_3	85	163–164°	$C_{19}H_{18}N_2O$ (290.4)	1690, 1620	1.95 (s, 3H); 2.33 (s, 3H); 2.63 (s, 3H); 7.2–7.3 (m, 4H); 7.4–7.5 (m, 5H)
c	4-CH_3	88	114–115°	$C_{19}H_{18}N_2O$ (290.4)	1685, 1620	1.90 (s, 3H); 2.33 (s, 3H); 2.60 (s, 3H); 7.13 (d, 2H, J=8 Hz); 7.3–7.4 (m, 5H); 7.77 (d, 2H, J=8 Hz)
d	2-Cl	90	152–154°	$C_{18}H_{15}ClN_2O$ (310.9)	1690, 1620	1.95 (s, 3H); 2.60 (s, 3H); 7.2–7.5 (m, 9H)
e	4-Cl	90	129–130°	$C_{18}H_{15}ClN_2O$ (310.9)	1685, 1625	1.90 (s, 3H); 2.67 (s, 3H); 7.20 (d, 2H, J=10 Hz); 7.3 (m, 5H); 7.90 (d, 2H, J=10 Hz)
f	4-Br	90	155–157°	$C_{18}H_{15}BrN_2O$ (355.2)	1690, 1620	1.93 (s, 3H); 2.60 (s, 3H); 7.33 (d, 2H, J=8 Hz); 7.4 (m, 5H); 7.92 (d, 2H, J=8 Hz)

[a] Yield of recrystallized product.
[b] The mass spectra and the microanalytical data were in satisfactory agreement with the calculated values: C ±0.30, H ±0.25, N ±0.30.

Table 2. 1-Aryl-3-phenyl-4,6,6-trimethyl-1,6-dihydropyrano[2,3-*c*]pyrazoles **(5a-f)**

5	R	Yield[a] [%]	m.p. [°C]	Molecular Formula[b]	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	H	70	110–111°	$C_{21}H_{20}N_2O$ (316.4)	2950, 1640, 1595	1.57 (s, 6H); 1.78 (d, 3H, J=1.5 Hz); 4.93 (q, 1H, J=1.5 Hz); 7.3–8.0 (m, 10H)
b	2-CH_3	65	102–104°	$C_{22}H_{22}N_2O$ (330.4)	2980, 1640, 1620, 1610	1.55 (s, 6H); 1.77 (d, 3H, J=1.5 Hz); 2.36 (s, 3H); 4.91 (q, 1H, J=1.5 Hz); 7.2–7.8 (m, 9H)
c	4-CH_3	65	95–97°	$C_{22}H_{22}N_2O$ (330.4)	2975, 1630, 1615, 1605	1.55 (s, 6H); 1.76 (d, 3H, J=1.6 Hz); 2.36 (s, 3H); 4.90 (q, 1H, J=1.6 Hz); 7.2–7.8 (m, 9H)
d	2-Cl	75	141–143°	$C_{21}H_{19}ClN_2O$ (350.8)	2980, 1630, 1590	1.50 (s, 6H); 1.81 (d, 3H, J=1.8 Hz); 4.88 (q, 1H, J=1.8 Hz); 7.3–7.9 (m, 9H)
e	4-Cl	80	102–104°	$C_{21}H_{19}ClN_2O$ (350.8)	2975, 1625, 1600	1.57 (s, 6H); 1.75 (d, 3H, J=1.5 Hz); 4.91 (q, 1H, J=1.5 Hz); 7.2–7.8 (m, 9H)
f	4-Br	60	126–127°	$C_{21}H_{19}BrN_2O$ (395.3)	2990, 1630, 1595	1.55 (s, 6H); 1.75 (d, 3H, J=1.5 Hz); 4.91 (q, 1H, J=1.5 Hz); 7.2–7.8 (m, 9H)

[a] Product isolated by chromatography on silica gel.
[b] The mass spectra and the microanalyses were in satisfactory agreement with the calculated values: C ±0.30, H ±0.20, N ±0.30.

due, which is chromatographed on silica gel (eluent: benzene) to give **5a**; yield: 2.22 g (70%); m.p. 110–111 °C.

$C_{21}H_{20}N_2O$	calc.	C 79.71	H 6.37	N 8.85
(316.4)	found	79.93	6.20	8.64

M.S.: m/e=316 (M^+, 30%); 310 (100).

U.V. (C_2H_5OH): λ=261 nm ($\log\varepsilon$=4.11).

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